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EFFICACY AND SAFETY OF RIFAXIMIN IN ACUTE GASTROENTERITIS IN CHILDREN: A META-ANALYSIS

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ABSTRACT

Background: Acute gastroenteritis is a major cause of morbidity and mortality in youth age in developing and developed countries, with a bacterial origin detected in a significant percentage of cases. A meta-analysis on the use of rifaximin in children in case of gastroenteritis has been performed.

Search Methods: All the available publications related on the use of rifaximin in infectious diarrhea in children has been included in this survey, included all the reports related to safety and adverse effects.

Data Collection and Analysis: All papers were selected and classified according to the QUORUM statement checklist. For meta-analysis, the Comprehensive Meta-Analysis Pro Version 2.2.64 was used.

Main Results: Meta-Analysis shows a higher number of healed patients (OR 1,93; p=0,054) in the rifaximin groups at the end of the studies, with a reduction of the mean number of stool/day (-2,021; p<0,001); more formed stool (OR 4,31; p=0,001); a shorter Recovery Time (OR 0,49; p=0,078), when compared to control groups. The microbiological tests performed after treatment have shown the persistence of 54% of the potentially most dangerous pathogenic bacteria in the children treated with diet and rehydration alone, in comparison with 11.2% in children treated with rifaximin or other antibiotic (chi square 7.4; p= 0.02).

Conclusions: According to our data, the use of rifaximin for bacterial diarrhea in children over 2 years may be fully justified in selected circumstances as in case of travelers' diarrhea, and in recurrent or relapsing diarrhea known or supposed to be caused by non-invasive rifaximin sensitive enteropathogens.

KEYWORDS : Rifaximin; gastroenteritis; diarrhea; meta-analysis; children; antibiotics; rehydration.

1. INTRODUCTION

Acute gastroenteritis (AG) is widely acknowledged as a major cause of morbidity and mortality in youth age in developing and developed countries [1,2], where – according to different surveys – medical assistance is asked almost for one of three children [3-7]. This percentage rise up to 50% in children under the age of 10 and to 70% under the age of 5 [7].

AG remains a primary cause of general practitioner (GP) intervention, Emergency Department (ED) admission, and hospitalization [8-10].

The burden associate to this medical condition vary according to the geographical localization. In US the cost of hospitalization secondary to diarrhea among children younger than 5 years is estimated at US $480 million, or a median cost of US $3586 per case. Indirect costs are mainly due to the loss of days of works/school for patients and caregivers, which are increased in case of hospitalization [7,11].

Although different health systems worldwide have a national survey program, a number of cases do not undergo etiological investigation. Yet a bacterial etiology can be detected in a significant percentage of cases, varying according to demographic distribution, geographic area, medical conditions, season and age group [7,11,12].

Almost one patient out of two, affected by AG in developed countries, made use of medicine prescribed by a doctor, advised by a pharmacist or a nurse, or self-prescribed [7].

Rehydration is considered the first therapeutic line for AG, being dehydration secondary to diarrhea a possible life threatening condition and still a major cause of death in developed counties or in undeveloped areas. In those settings, Oral Rehydration Therapy (ORT) is largely recommended (WHO). Nonetheless, in developed country the role of oral, nasogastric and intravenous (IV) rehydration and the regimen to be used for those therapies is still under discussion [13,14].

Antibiotics are not considered a standard therapy for diarrhea, and although the admnistration of this type of drugs in children – especially when different age groups are considered – is still controversial, their use in selected conditions has been proven to be useful [11,15-21].

Rifaximin is a non-absorbable antibiotic locally active at gastrointestinal level with a broad spectrum of antibacterial activity. It has been on the market in several EU and non-EU countries for several years, and as far as infectious diarrhoea is concerned, its efficacy and safety have been proved in adults [20,21].

Being children a highly affected group, and the one that is likely to develop major complications secondary to AG, the use of this molecule in this age could in selected conditions appear appropriate. Nonetheless, efficacy of rifaximin is still under discussion, as no statistically significant evidences – when individually considered – have been published so far. Therefore, the aim of this meta-analysis was to evaluate efficacy and safety of rifaximin plus diet and rehydration in comparison with diet and rehydration alone, or added to placebo, or to other antibiotics, when used in children of different age classes.

2. MATERIALS AND METHODS

Meta-analysis has been performed according to indications that come from the PRISMA statement [22]. During the planning of the study, we produced a research protocol that has been subsequently used during the phases of the search strategy, study selection, data extraction, assessment of study quality, and analysis of the data.

2.1 Search strategy

All the studies published related on the use of rifaximin in infectious diarrhea in children has been included in this survey, regardless of their language or the publication process status. Because the number of publications on rifaximin in children is limited, and taking into account the recommendations of the recent literature [23] – which suggests an extensive use of all the available sources of medical publications – several sources have been inquired. The words "rifaximin", "diarrhea" (and its variant or misspelled words), "diarrhea therapy" have been searched on MEDLINE database, EMBASE, SCOPUS (including all areas: Life Science, Health Science, Social Science, and Physical Science), Clinical Trials.gov and the Cochrane Library. The words "children", "pediatrics", "paediatrics", "paediatric" have also been searched in combination with "rifaximin". Where available, trials have been searched also for age groups. Additional trails have been requested directly form chemical industries producing rifaximin in order to add possible unpublished regulatory dossiers or papers published in less relevant articles that maybe not be found on the main international databases. Some older papers, currently not available on the Internet, have been requested to single Authors that have kindly offered their works. All the available publications and reports related to safety and adverse effects of rifaximin in children have been considered.

2.2 Study selection

All papers were selected and classified according to the QUORUM statement checklist [24] (see Figure 1); eligibility criteria adopted for children in each clinical

trial (CT) have been also taken in account, as well as the comparable general characteristic of the analyzed studies (age, sex, dose, treatment duration, parameters for efficacy and safety evaluation, lab-tests).

2.3 Data extraction and assessment of study quality

Considering the great heterogeneity of clinical criteria for the evaluation of the clinical course of AG, we decide to analyze preferentially data congruent with the issues for measurement of acute diarrheal disease in childhood [25]. According to WHO, diarrhea is defined "as having loose or watery stools at least three times per day, or more frequently than normal for an individual" [26], considering as a different feature the presence of mucous or bloody stools. The following definitions have been thus considered in this meta-analysis:

a) *Diarrhea definition*: presence of 3 or more loose or watery or liquid or semi-liquid stools in 24 hours;

b) *Stool Output*, also described as "*Bowel Movements*" or "*Stools/Day*": the mean number of evacuations per day at the begin and at the end of the study.

c) *Recovery Time* (RT), also described as "*Time of Diarrhea Duration*": days for complete recovery according to WHO diarrhea definition (stool output lower than 3/day) plus absence of mucous or blood in stools.

d) *Time for Complete Healing*: considered as absence of diarrhea, fever and vomiting.

e) *Stools consistency and Time to Last Unformed Stool* (TLUS). This datum in part overlaps the previously reported RT. However, different Authors included (or not) these parameters both in the single evaluations of efficacy at the end of the study (those data were excluded from meta-analysis) and/or in the evaluation of the Healing Time, or reported them directly as "number of patients" or "number of times".

f) *Therapy failure*: number of patients considered not cured at the end of the study, where the failure is defined as (a) presence of unformed stools/mucous or bloody at the final visit, (b) presence of symptoms or (c) treatment failure secondary to the physician's professional judgment

g) *Dropout*: The total number of drop outs (due to side effect or to other reasons) was considered in the analysis. Meta-analysis did not take into account the studies with a value of "0" related to the number of dropouts in both groups.

For these reasons, we made different attempts to meta-analyze only those parameters that could be objectified according to a properly established definition and that directly refer to individual patients. If some ranked variables (e.g. stools consistency) were reported with different scale or with different direction for improvement (ascending or descending), they has been standardized with a proportional model. Time intervals were treated as continuous variables (using mean and variance) if expressed in hours (even when they were transformed in days) or as interval measurements in other cases (i.e. days – 1, 2, ... – without further details).

The days of recovery of normal "alvus" reported in the different studies were uniformed (duration of diarrhea in number of days or in number of hours); the presence of unformed or mucous stools at the end of the study (reported by one study only) were included in the final evaluation as inefficacy of the treatment considered.

One study (Lombardo) reports incomplete data on 3 different groups (different rifaximin formulation in children of different age classes) and the data of recovery are based on the few information available. For this reason this study was not included in some analyses.

The quality of the trials with usable information has been evaluated according to the Jadad scale 27. Jadad score for each paper included in the meta-analysis is reported in Table 1.

2.4 Meta-analysis and statistics methodology [28]

For the meta-analysis, the Comprehensive Meta-Analysis Pro Version 2.2.64, 2011 (www.meta-analysis.com) was used. In order to estimate the effect size for numerical continuous variables the analysis for unmatched groups, using means, standard deviation and sample size has been performed on controlled clinical trials (CTs). The method to post-therapy data and in some cases values on average before therapy has been applied, with an expected "null" difference when good randomization and homogeneity existed between rifaximin and control group.

For dichotomous variables effect size has been considered both for events and sample size or for non-events plus sample size; we enclosed the main results (and particularly the results obtained with a properly defined category of response-to-therapy, i.e. children completely recovered and children unresponsive to therapy). Undefined intermediated results such as "fair", "sufficient" or "good" therapeutic response, were not consider for the evaluation.

In few cases, we derived from the studies the mean difference of semi-quantitative variable (days of recovery, 1-2-3 etc., or hours of recovery), estimated the common standard deviation and performed the analysis on this basis (Δx, cSD, sample size).

When appropriate, we computed odds ratios, z test and p, or the Hedges's standardized coefficient, to eliminate scale differences [29,30].

The low number of the available studies and the type of patients, limit the possibility to obtain valid results sub-classifying the trials on the basis of type of randomization, evaluation of dropouts and/or withdrawals, by Jadad 5-point scale or by other similar systems [27,31].

Therefore we did not perform any type of analysis of sub-group of patients, both because of the number of children treated and the absence of univocal criteria for sub-group identification; moreover, sub-group analysis is not suggested by guidelines on correct use of meta-analytical methods [32,33].

For this statistical analysis, the following parameters have been considered:

- Type of control group
- Enrollment criteria
- Main efficacy criteria
- Sex distribution
- Age
- Patient number
- Drug dosage
- Treatment length

For statistical tests, we considered the total number of patients enrolled and not the number of patients that finished the study with an intention-to-treat-like approach.

3. RESULTS

3.1 Search and selection results

Thirty-one potentially relevant studies were identified, among over 410 paper published on rifaximin antibiotic therapy; Among those, fifteen do not contain original clinical data. Of the sixteen studies potentially eligible for meta-analysis, eight were selected (Table 1) [34-41] and eight were excluded mainly as they referred to trials in which AG was not the main diagnosis [42-49]. In two of the excluded studies [42,43], data were consistent but age groups were mixed and it was not possible to heave off the pediatric data. All the included articles contained statements about ethical committee and/or informed consent.

3.2 Description of the included studies

Valid data have been obtained for a total 401 children treated: 233 with rifaximin (109 males and 124 females) and 168 (81 males and 87 females) with diet and rehydration and/or placebo and/or antibiotics (neomycin, neomycin plus bacitracyin, paromomycin). In all the included studies, microbiological assessments on stools have been carried out both at the beginning of the treatments to verify the etiology of the enteritis and at the end of the treatments to evaluate the eradication of the pathogenic bacteria.

Table 2 shows the demographics of the children included in the eight studies and the type of control drug if present. The overall age sex distribution in rifaximin and control subjects is balanced; the same applies to single studies distributions.

3.3 Meta-analysis

The estimates of overall mean age resulted of 4.6 for R and 4.7 yrs. for C. Assuming a stochastic age distribution, we estimate that the first quartile of age include about n. 58 and n. 42 patients with age <3.3 and <3.4 year for rifaximin and control groups respectively. No one neonatal patient was enrolled in these studies.

The rifaximin used dose is homogeneous among the studies and compatible with the standard one suggested by the producer, ranging from 15 to 30 mg/kg/day. Rifaximin and the control drugs were always administered following producer's recommendation (2-4 administration daily). The mean length of the studies resulted of 4,3 days (3 to 5).

Both fixed and Random-effect models have been used, but no significant differences have been observed. The results of the meta-analysis have been consequently showed only by fixed-effect model graphics. The box-areas represented in the figures are proportional to the relative weight of each study.

Post-therapy effect expressed in number of stool/day. The mean number of stool per day pre- and post-rifaximin therapy is showed in Figure 2 (within group analysis, overall: Standard difference in means -2,021 95% IC -2,32 -1,79). For two studies the mean values have been estimates. In the Figure, Lombardo's case-report is subdivided in three age groups as per original article. The data are relatively homogeneous, excepting for Sanfilippo's article. The standard difference in the means of three age-classes of Lombardo's article are widely overlapping.

Formed stools in patient treated with rifaximin. In controlled studies, the number of patients with formed stools (without mucous, blood, watery) at the end of the study resulted significantly higher in the rifaximin groups than in control groups

(Figure 3) The figure shows the odds ratios resulting from fixed effect model: overall odds ratio 4,31 (1,77-10.4), p=0.0012; the results are similar with random-effect method. The Frisari's study, against paromomycin, produces non-significant differences between the two antibiotics.

The meta-analysis of number of non-responders, namely patients with diarrhea or unformed and/or mucous and/or bloody stools at the end of antibiotic therapy (data from the studies by Beseghi, De Castro, Frisari and Sanfilippo) provided mirror results in favor of rifaximin: odds ratio at the end of the study =0,24 (IC95% 0,08-0,7), z=-2,59, p=0,0094 (data not showed).

Recovery time in patients treated with rifaximin. The RT expressed in days (evaluated in 5 articles) is showed in Figure 4. As suggested by the expert system, the analysis was performed on the mean differences using a common standard deviation model. The overall odds ratio resulted 0,48 (0,23-1,08); in individual studies, RT occurred 1-2 day earlier in the rifaximin group .

Meta-analysis of times in days of last unformed stools produced similar results (both fixed and random effect approach was performed, considering the data as non-continuous interval measures); comparable data come from six articles (Stornello's paper was included over the articles quoted in Figure 4), with an overall odds ratio of 0,67 (0,34-1,3) z=-1,15, p=0,2); one of the three placebo-controlled trials reported a significant result in favor of rifaximin (odds= 0,16, p=0,041) and other two placebo-rifaximin trials gave an odds ratio < 1 (Sanfilippo and Macias). Unsurprising, the odds ratio of comparison between rifaximin and neomycin, paromomycin and neomycin+bacitracin were around 1.

Patient considered healed at the end of the studies. In Figure 5 fixed-effect graphs are reported of the number of patients in which therapy was completely successful (healed) on the basis of extensive definition reported in material and methods. The data are not available for all studies, although some Authors report individual evaluations (regulatory dossier) or "personal" cumulative evaluation ("good" or "fair" efficacy or similar, not considered). The cumulative odds ratio is in favor of rifaximin: 1,93 (0,99-3,78) with a z value of 1.93 (p=0,054).

The evaluation of number of patients not cured (therapy failure) at the end of the studies are shown in Figure 6. The results are mirroring to the previous one (Figure 5) and statistically significant. The cumulative odds ratio of number of not-cured patients, evaluated by fixed-effect estimate, resulted of 0.39 (0,17-0,91), z=-2,18, p=0,029 (random effect: z=-2,59, p=0,009).

All the studies reported data about: individual adverse events (Aes); withdrawals or dropouts; global evaluation of safety; and laboratory tests (however, the analytical result are not always published and in some papers we found only synthetic comments on lab test results). Table 3 summarizes the safety results of analyzed studies: overall 3/233 children (1,3 %) showed minor complaints (2 cases of vomiting attributed to drug and 1 of gastric intolerance). No children experienced major adverse events or alterations of the laboratory tests (usually: blood urea nitrogen or blood creatinine, hematocrit and RBC/platelets/white blood cell count, hemoglobin, hepatic enzymes, urinalysis, blood Na+/K+, fasting blood sugar, others). Among active-drug controls, epigastric pain/vomiting occurred in 1,6% of patients; no other main complaints were reported.

Only one patient in the rifaximin group withdrew for AEs (Ambrosioni's article, for gastric intolerance); one children with vomiting in the Macias's study, withdrew for "ethical reasons" (2/233; 0,85%); drop-out for AEs among children treated with other antibiotics resulted of 1,7%. However, we analyzed the odds ratio of the number of all-causes withdrawals (spontaneous withdrawal or poor compliance, viral agent detected during the study, symptoms worsening or AEs, as reported) in controlled studies: common effect OR 0,41, 95% IC 0,09-1,8, z=-1.17, p=0.242).

No relapsing or rapidly worsening cases during the study were reported in rifaximin-treated children; however, in all the studies the follow up was stopped at the end of clinical trials and very few information are available on medium term clinical course. Moreover, one study (De Castro) was carried out in children with recurrent diarrhea associated with chronic genitourinary disorders, and results were comparable with those of the other studies (Fig. 2).

Microbiological tests performed before and after rifaximin therapy are not useful for meta-analysis. However, the persistence of the potentially most dangerous pathogenic (E. Coli, Shigella and Salmonella) bacteria is 54% in the children treated with diet and rehydration alone in comparison with 11.2% in those treated with rifaximin or other antibiotic (chi square 7,4; p= 0,02), without significant differences between the type of antibiotic used.

4. DISCUSSION

AG is a short course, self-limiting medical condition. Yet, because of its high frequency and the related burden in term of direct and indirect costs, it can be considered as a major cause of morbidity in developed and developing countries, with a high impact on the health systems and the whole society.

Higher costs are associated to the length of the disease together with young age. Those same factors also produce an increased number of medical intervention (patients or caregivers seeking for assistance); use of self-prescribed (and paid by the patient) and prescribed (and paid by the health system) medication; hospitalization [7]. An overall reduction of the duration of the disease is consequently due in order to decrease its burden.

Although a viral etiology is common in children, in a significant number of cases the bacterial origin can be detected. According to literature [50], patients with bacterial diarrhea should be treated with antibiotics if they are: debilitated (particularly with malignancy); immunosuppressed; have an abnormal cardiovascular system; have valvular, vascular, or orthopedic prostheses; have hemolytic anemia; or of extremely young or old age. Antibiotic treatment is also advised for those with prolonged symptoms and those apt to relapse.

In addition, the Clinical Guideline of April 2009 produced by NICE [51] on "Diarrhea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years", underlined that even for very common and theoretically effective antibiotics, the clinical trials on children are very few and with several methodological limitations. Because of the important documentation related to the use of antibiotics for the treatment of travelers' diarrhea in adults, the most significant of which presently includes rifaximin [20,21], this guideline emphasizes that although "there was no clinic trial evidence on the treatment of traveler's diarrhea in children, the GDG (Guideline Development Group) considered that trials in adult patients were relevant, and these showed evidence of benefit from antibiotic treatment. It was therefore agreed that in such cases consideration should be given to seeking specialist advice regarding antibiotic treatment in children presenting with acute diarrhea shortly after return from overseas travel" [21].

The role of rifaximin as a non-absorbable antibiotic locally active at gastrointestinal level with a broad spectrum of antibacterial activity have been considered to establish whether the use of this antibiotic can be considered safe in children and effective in the reduction of the length of the disease.

Despite the different criteria and clinical settings of the studies, the bacterial origin of the diarrhea was the characteristic which was present in all studies. The use of antibacterial drugs have shown a significant reduction of the persistence of the pathogen when compared with diet and rehydration treatments alone. The most commonly isolated pathogenic agent was *Escherichia* Coli (*E. coli*). *E.coli* and other non-invasive enteropathogens were shown in adults to be the most clinically sensitive bacteria to rifaximin. In-vitro studies show that also enteropathogens of invasive type (such as *Salmonella* and *Shigella* species) are highly sensitive to rifaximin [52,53]. This discrepancy is attributable to the negligible absorption of rifaximin that from one side allows high drug concentration to be achieved on intestinal mucosa and on the other side prevent the drug to be in contact with enteropathogens if they invade the intestinal wall (as clinically shown by high fever and/or blood in stool). In fact rifaximin was shown to be effective in preventing shigellosis in healthy volunteers receiving rifaximin before being challenged with Shigella flexneri, therefore suggesting an in-vivo protection before the microorganism invades the intestinal wall and is no longer in contact with the luminal antibiotic [21,53].

Aside its theoretical effect, supported by the single studies, our meta-analysis demonstrates a good efficacy of rifaximin in children over 2 years of age, when compared with non-pharmacological support and other treatments, in terms of: reduction of the number of stools/day; number of patients presenting with formed stools at the end of the treatment; reduction of the RT; and number of patients considered cured at the end of the study. As the majority of the enrolled children aged more than 2 years, for younger babies neither adequate nor sufficient efficacy and safety data are available.

Some limitations affect our analysis: differently from the ones related to adults, the studies assessing the role of rifaximin in the treatment of infectious diarrhea in children are almost all older than 15 years and included limited sample sizes, implying consequently both methodological limitations and not conclusive results from single studies.

Aside from the Macias' study 41 few children have been enrolled in each trial, so that the overall number of patients considered is limited. Because of that could the study did not support any sub-group meta-analysis on specific clusters – such as doses used, or age groups. In some of the available papers the omission or incomplete description of the enrolled patients and their outcomes have to be highlighted.

Besides, although in our study we refer to WHO indications, there are still not shared conclusions on what complete recovery from AG is, as the same definition of diarrhea and of its resolution remain controversial [25].

On the other hand, the aim of this meta-analysis was to try to overcome the limitations that lied within each single study, by obtaining data from the whole pediatric population involved in the treatment of infectious diarrhea. However, even considering this limitations, the data from this meta-analysis suggest that the clinical response to rifaximin, intended as a reduction of the length of disease is actual. Reducing the number of days of diarrhea means not only an early recovery of the well being of young patients, but also a reduction of the burden for their

caregivers and health systems, affecting direct and indirect costs related to this disease.

In relation to safety, our study detected only few dropouts which are unlikely attributable to the drug, as also stated by individual Authors/Investigators. This data on safety and tolerability of rifaximin in children should be assessed together with the evaluations carried out on the corresponding post-marketing safety update report (PSUR)[54] on rifaximin and the good clinical practice (GCP) studies in adults. From the examination of all these documents an acceptable risk/benefit ratio emerges for the use of rifaximin in children.

The available number of data do not allow to assess whether the use of rifaximin can be considered safe in newborns and in children under the age of 2 years, so that in particular these age groups would be worth to be specifically evaluated in further clinical trials.

CONCLUSIONS

Antibiotics for the treatment of acute diarrhea both in adults and children are usually considered for selected condition [51]. Because of its low systemic adsorption, broad spread of activity, safety, relatively lack of adverse reactions, and low impact on the normal bacterial flora of the bowel, in non-invasive cases "rifaximin matches the criteria for an ideal agent for the treatment of infectious diarrhea" [55]. Moreover, recent articles underline the anti-inflammatory effect and a minimal negative effect on the overall composition of the gut microbiota [56].

This study evidences that the conclusions of the Authors of the articles included in the analysis appear consistent: according to our data, the use of rifaximin in children for the treatment of selected AG conditions appears fully justified. In particular, the use of rifaximin in children can be indicated in specific cases of bacterial infectious diarrhea, such as in case of travels' diarrhea; augmented risk of relapses; surgical patients; debilitated or chronic patients in which the reduction of the length of the disease can be recommended.

The analysis also confirms the tolerability of the use of rifaximin in children, with a very low number of drop outs, scarcely imputable to the drug. Further studies are recommended in the future to better assess the consistency of this findings.

COMPETING INTERESTS

This work was used as part of a consultancy funded by AlfaWassermann (Prof Gaddi only); however, the authors have no financial interests or economic incentives pertaining to Alfa Wassermann. Alfa Wassermann did not contribute to the writing, analysis, or interpretation of research findings. All of the data included in the present article were extracted from peer-reviewed published articles or published research currently available for review, and all of the analyses performed are transparent and reproducible.

AUTHORS' CONTRIBUTORS

CF wrote the first draft of this manuscript and contribute to the data analysis and interpretation. GAV designed the study, collected data, takes responsibility for the integrity of the data and the accuracy of the data analysis, and is the guarantor of the manuscript. All of the authors checked the data and the references for consistencies, and contributed to the intellectual content of the manuscript and its final version.

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The QUOROM statement flow diagram showing the inclusion/exclusion process used to retrieve usable information from the selected papers.

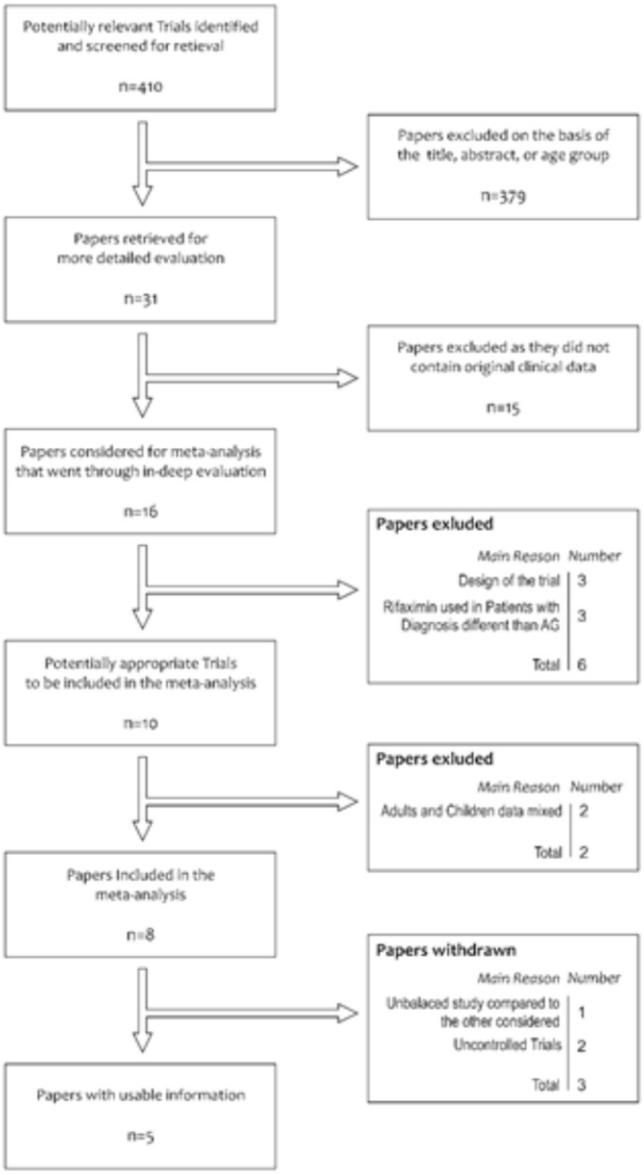

Figure 1. QUOROM statement flow diagram

Standard difference in means of stools/day, before and after rifaximin therapy. Lombardo's data are subdivided, as per article, by age (a=0,2-1,7; b=1,8-4,0; c=5,0-12,0 years). A= Rifaximin, B= Controls

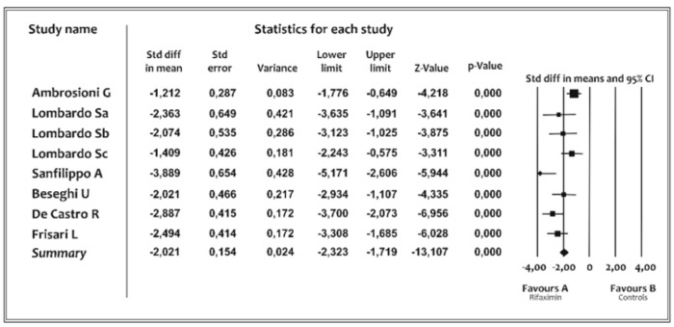

Figure 2. Stools/day outcomes

Odds ratio (OR) and 95%IC, fixed-effect meta-analysis of number of patient with formed stools at the end of therapy in controlled studies. A=Controls, B=Rifaximin.

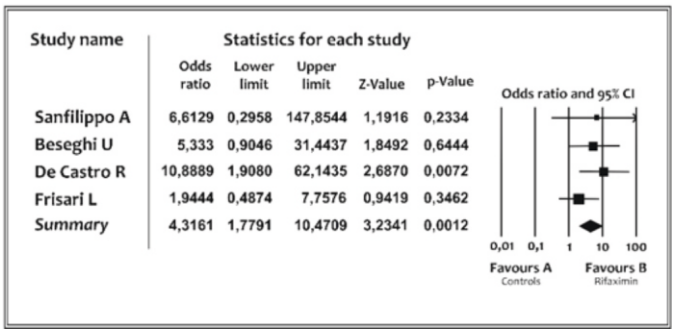

Figure 3. Formed stools at the end of treatment

Odds ratio of recovery times in days in five controlled studies. See text. A= Rifaximin, B= Controls.

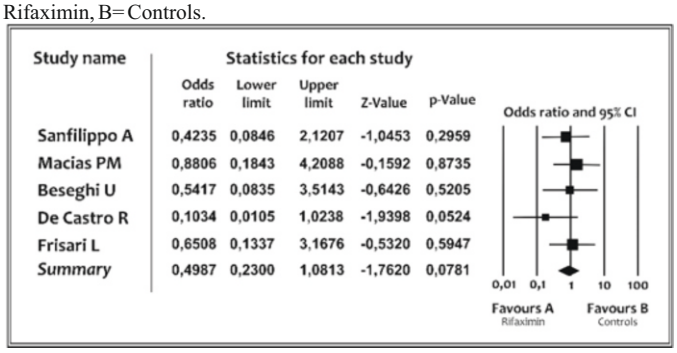

Figure 4. Recovery time

Odds ratio of number of patients completely healed at the end of the study. Placebo or active-drug controls= A, Rifaximin=B. See text fur further details.

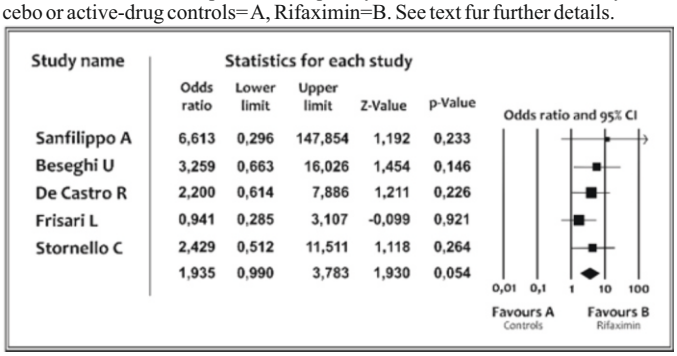

Figure 5. Patients considered healed at the end of the study

Odds ratio of number of patients not-cured at the end of the study. Rifaximin=A; S or active-drug controls= B. See text fur further details

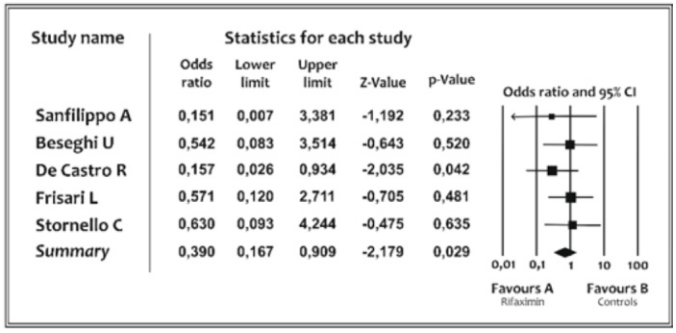

Figure 6. Patients not-cured at the end of the study

Table 1 Main characteristics of studies included in the meta-analysis.

#	First Author	Journal	Year	Ref.	Design	Children enrolled	Diagnosis	Jadad	Microbiol. Analysis	Institution
A	Lombardo S	Farmaco (Prac)°	1983	34	Open Label, Uncontrolled	31	Acute and Chronic bacterial diarrhea	1	yes	Gen. Hosp. Dept of Pediatrics
B	Ambrosioni G	Clinica Pediatrica °	1984	35	Open Label, Uncontrolled	21	Acute bacterial diarrhea	1	yes	Gen. Hosp- Pediatric Division
C	Sanfilippo A	Med Praxis	1984	36	Randomized, placebo controlled, double blind	37	Acute diarrhea	3	yes	Gen. Hosp. Dept of Pediatrics
D	Stornello C	Med Praxis	1987	37	Randomized, active-drug controlled	40	Acute diarrhea	2	yes	Gen. Hosp. Dept of Pediatrics
E	Frisari L	Curr Med Res Opin	1997	38	Consecutive patient randomization, active drug controlled	49	Acute diarrhea	3	yes	Gen. Hosp. Pediatric Surgery Dept
F	Beseghi U	Eur Rev Med Pharmacol Sci	1998	39	Consecutive patient randomization, active drug controlled	31	Acute diarrhea	3	yes	University, Ped. Surgery and Ped. Gastroent. Dept.
G	De Castro R	Curr Ther Res Clin Exp	1998	40	Randomization (2:1) against rehydration therapy	46	Acute recurrent diarrhea ǂ	3	yes	University, Pediatric Urology Dept
H	Macias PM	Ped infect Dis J	2002	41	Balanced-block randomization, placebo controlled	146	Acute diarrhea	3	yes	National Institute of Pediatrics
			° Regulatory dossier available ǂ With urethrovescical reflux and irritable bl adder							

Table reports the title and the journal of the studies included in the meta-analysis, together with their characteristics, included the number of patients enrolled, and the quality assessment (Jadad score)

Table 2 Patients enrolled in the studies.

#	Male		Female		Age		Type of patient	Type of control
	Rifaximin Group	Control Group	Rifaximin Group	Control Group	Rifaximin Group	Control Group		
A	17	-	14	-	0,2-12	-	Inpatients	none
B	9	-	12	-	0,3-5	-	Inpatients	none
C	10	7	10	10	2-8	2-8	Inpatients	Placebo/Diet (including oral rehydration)
D	12	9	8	11	3-12	2-13	Inpatients	Neomycin/Rehydration when strictly necessary
E	13	13	11	12	4-8	3-6	Inpatients	Paromomycin
F	5	7	9	10	3-5	2-5	Outpatients	Neomycin+Bacitracin
G	10	5	20	11	3,1-5,4	3,5-4,9	Inpatients	Oral rehydration
H	33	40	40	33	0,5-5	0,5-5	Outpatiens	Diet and oral rehydration
All	109	81	124	87	-	-		

Demographics, number of patients and number of controls subdivided by gender of the children enrolled in the different studies included in the meta-analysis. The age ranges of the patients included in the studies are expressed in years or in fraction of year. Paper # A (Lombardo) subdivided patients by age (0,2-1,7; 1,8-4,0; 5,0-12,0 yrs).

Table 3 Safety of Rifaximin according to the studies included in the meta-analysis.

Author	N.	Safety parameters	Safety in Rifaximi-treated patients
Ambrosioni G	21	AEs, Lab-tests	Lab-test in the range of normality. Good safety except in 2 cases (vomiting and gastric intolerance)
Lombardo S	31	AEs, Lab-tests	Lab-test in the range of normality. No adverse event
Sanfilippo A	20	AEs	No adverse event. Tolerance always "very good"
Macías P M	73	AEs	Good safety and tolerance; one cases of vomiting.
Beseghi U	14	AEs, Lab-tests	No AEs or Lab clinically relevant abnormal value
De Castro R	30	AEs	No adverse events
Frisari L	24	AEs, Lab-tests	Absence of clinically relevant lab-abnormalities and no AEs reported
Stornello C	20	AEs, Lab-tests	Good safety; one case of vomiting; no abnormal values at lab evaluations.

Table shows the summary of tolerance results in rifaximin treated patients, as highlighted by the different authors of the studies included in the meta-analysis. N. refers to the number of patients treated with rifaximin during the studies. Safety parameters refers to the criteria used to assess the level of tolerance in treated children (AE=adverse event daily checked; Lab-test= safety laboratory test before and at the end of therapy).

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